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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,050	10/12/2004	Masami Kusaka	Q101060	6207

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EXAMINER	
MAEWALL, SNIGDHA	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,050	KUSAKA ET AL.	
	Examiner	Art Unit	
	Snigdha Maewall	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3 and 5-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-3 and 5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

1. Receipt of amended claims and arguments filed on 05/26/09 is acknowledged. Claims 1 and 8 remain withdrawn. Claim 4 remains cancelled.

Claims **2-3 and 5-7** are under prosecution.

New rejections have been made in this Office action, accordingly the Office Action is being made Non-Final.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement Rejection

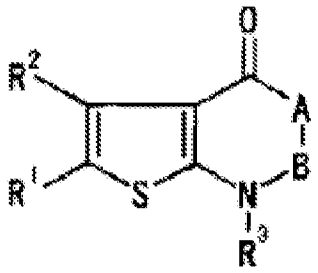
3. Claims **2-3 and 5-7** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a limited number of compounds for treating hot flashes does not reasonably provide enablement for the trillions of possible structures claimed for treating hot flashes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to *make and use* the invention commensurate in scope with these claims. For instance, with respect to the *making* aspect of the invention, of the multiple possibilities for R1

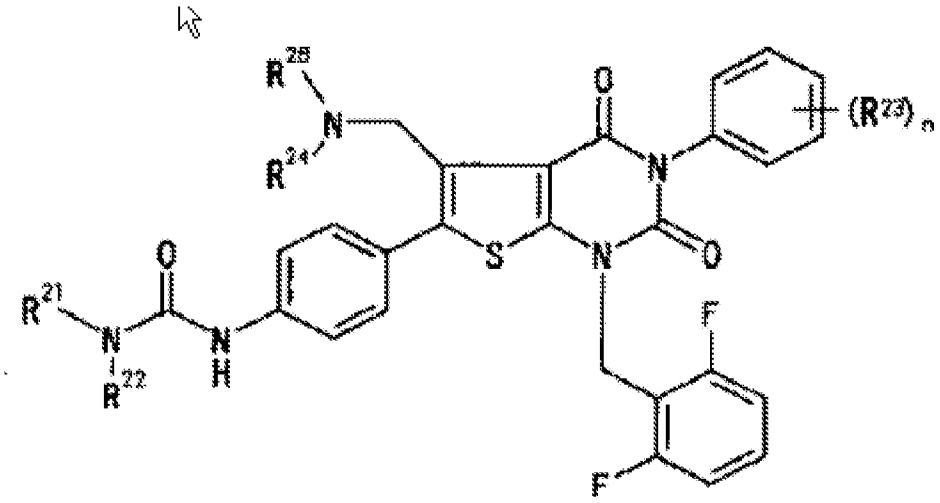
and R2 and R3 and p and q groups in claim 5 and several substituents in claim 6, the specification is enabling for the making of only few possibilities but not all the possible structures that are claimed. Likewise, in support of the biological activity of the claimed compounds (i.e., *potential* utility for treating hot flashes), the disclosure is limited to describing only single possibility of single compound (example 7) with specific substituents linked to treating hot flashes.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The breadth of claims: The claims are drawn to compounds of the formula *(elected group),*





With multiple possibilities of substituents as disclosed in claims 5 and 6.

The side groups having substituents layered on top of substituents encompassing trillions of possible compounds and all of such compounds have been claimed in treating hot flashes. The substituents vary widely in size, molecular topology, properties such as acidity and basicity chemical and physical properties rendering the breadth of the claims wide. The disclosure lacks guidance linking various possible compounds with various substituents with hot flashes. No technical data has been provided for treating hot flashes with every compound. In the absence of specific compounds or groups of compound and their correlation in treating hot flashes, one skill in the art would undergo undue experimentation to practice the invention.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the art of organic and medicinal chemistry, it is noted that each embodiment of the invention is required to be individually assessed for viability.

The amount of direction provided by the inventor and the presence or absence of

working examples: The direction and working example provided in the specification is extremely limited.

Specification only provides enablement for specific compound such as prepared in example 7 on page 97 and utilizing such compound in treating hot flashes. It is not seen where in the specification, enablement is present for making any other compounds besides few and with variables and linking the claimed compounds with hot flash treatment.

The specification does not provide citations (commercial or literature) for procuring the starting materials usable that could substitute for the lack of working examples with respect to non-enabled substitutions.

The specification does not disclose biological data (treating hot flashes) for any of the claimed compounds.

The state and the predictability of the art: With regards to making of the compounds, in spite of major advances in protecting group strategies and organic synthesis, the state of the art is unpredictable as to functional group compatibility during many chemical transformations. As such, one of ordinary skill in the art attempting to make applicant's compounds would be faced with trial and error experimentation to arrive at a viable chemistry sequence to introduce the invariants present in the formula. The existence of such unpredictability and uncertainties would prevent one of ordinary skill in the art from accepting the only process present in the specification on its face as universally applicable for all the substitutions claimed.

The quantity of experimentation: For the reasons presented above, there is a

substantial gap between what is taught in the specification and what is being claimed. *Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".*

Response to arguments

4. Applicant's arguments filed 05/26/09 have been fully considered but they are not persuasive.

Applicants argue that the instant specification teaches the compounds of claim 7 and also teach preparation. Example 1 test compounds are within the scope of claim 7 and describe an assay for determining the activity of the compounds. Therefore one of ordinary skill will be able to make and use the invention without undue experimentation. Applicant's arguments are not persuasive because applicants have not provided any correlation between each and every compound in treating hot flashes. The specification only teaches example 7 in decreasing estradiol concentration, however no data has been shown in treating hot flashes with the claimed compounds. Only the statement is not enough to substantiate the claimed invention. No experimental data has been provided involving treatment of hot flashes with the claimed compound comprising various substituents. Applicant argues that the specification provides assay for determining the activity of the compounds and thus it'll be within the purview of a skilled

artisan to prepare and use the claimed compounds. Applicant's arguments are not persuasive because as applicants themselves say the disclosure provides an assay ., an assay is not just sufficient to assess the validity of treating hot flashes. The disclosure only indicated that estradiol was decreased and hot flashes were treated., no substantial data has been provided to correlate each and every compound that is within the scope of claim 7 with treating hot flashes. Therefore in view of the disclosure one of ordinary skill would undergo undue experimentation to practice the claimed compounds in treating hot flashes. The rejection will be maintained.

Claim Rejections - 35 USC § 103

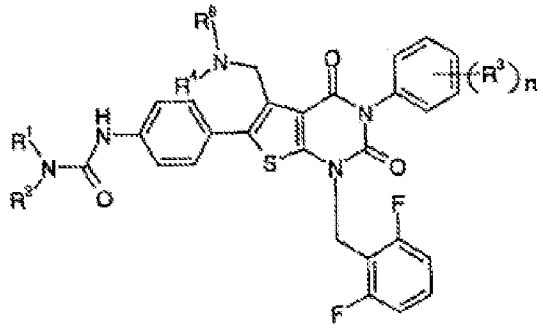
5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 2-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuya et al. (US 6,297,379) in view of Takayoshi et al. (Brain Research, 754 (1997) 88-94. (Submitted in IDS) and further in view of applicants admission in instant specification page 3.

It is noted that Furuya et al. (US 6,297,379) is the National Stage of PCT publication WO00/56739 to Furuya et al. published on September 28, 2000.

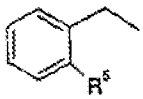
Furuya et al. teach a method of treating sex hormone-dependent diseases comprising administering a compound of formula (I):



(I)

,

where R^6 is:



(abstract).

The compound of formula (I) has excellent gonadotropin releasing hormone (GnRH) antagonizing activity (abstract).

Regarding entering the brain as recited in instant claim 2, it is well known in the art that gonadotropin-releasing hormone (GnRH) is synthesized and released by the hypothalamus and is responsible for the release of follicle stimulating hormone (FSH) and lutenizing hormone (LH) from the anterior pituitary. It is also well known in the art that the anterior pituitary and hypothalamus are located at the brain stem.

Furuya et al references teach that the disclosed compounds are useful for preventing and/or treating sex hormone-dependent cancers, prostatic hypertrophy, hysteromyoma, endometriosis, precocious puberty, amenorrhea, premenstrual syndrome, multiocular ovary syndrome and acne, which are conditions that are caused, **exaggerated** or maintained by sex hormones. In other words, the

conditions taught by the Furuya et al references are conditions **where sex hormones are increased.**

Furuya et al. do not specifically teach treating hot flashes, Takayoshi et al. teaches gonadotropin-releasing hormone antagonism and its relation with treatment of hot flashes with such agents (see the whole article and the following paragraph). Takayoshi et al. teach:

> Gonadotropin releasing hormone (GnRH), synthesized in the hypothalamus and secreted into the portal vein in the median eminence, plays important roles in regulating the menstrual cycle [9] and promoting lordosis behavior [23].

> It is the GnRH that is thought to play a critical role in producing them [2,13]. Because skin vasodilation is a heat-dissipating thermoregulatory response and hot flushes tend to occur in the thermal condition in which normally skin vasodilation does not occur [3], hot flushes can be considered a malfunction of thermoregulation [13]. We therefore examined the central effects of GnRH on the thermoregulatory vasomotion of female rats. Both the hippocampus and septohypothalamic area contain high concentrations of GnRH receptors [1,8,13], but because the hippocampus does not seem to make a major contribution to thermoregulation [21], we focused on the effects of GnRH applied to the septal area and hypothalamus. All the rats in this work were ovariectomized to assure a stable hormonal condition, and we examined the central effects of GnRH not only on the skin vasodilation elicited by warming the preoptic area (PO) of anesthetized rats, but also on the skin vasomotion and core temperature of unanesthetized and unrestrained rats.

Takayoshi tests the effects of administering GnRH and Antide, an antagonist of GnRH on thermoregulatory skin vasomotion. Takayoshi teaches the treatment of hot flashes with a specific compound, i.e., Antide, which is an antagonist of GNRH. Thus the state of the art teaches that gonadotropin releasing hormone (GnRH) antagonist treats hot flashes.

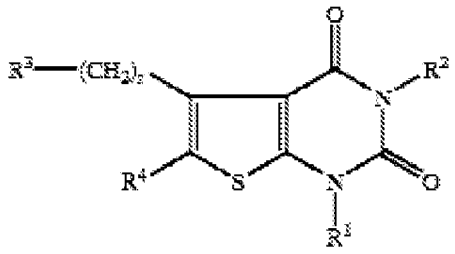
Instant specification discloses lowering the sex hormone level decreases the negative feedback of the sex hormone and promotes synthesis and secretion of GnRH (gonadotropin releasing hormone). GnRH stimulates synthesis and secretion of LH and FSH to enhance their blood concentration. Therefore, various climacteric disorders including **hot flash may be caused by increase in the GnRH, LH or FSH level.** From an experiment of administration of GnRH or GnRH and an antagonist thereof into the brain of a rat, it was suggested that increasing GnRH level was involved in manifestation of hot flash and an antagonist of GnRH might suppress it. (Brain Research 754 (1997) 88-94.) (See page 3).

It would have been obvious to one of ordinary skill in the art at the time of instant invention to utilize gonadotropin releasing hormone antagonists as taught by Furuya et al. in treating hot flashes because Takayoshi teaches utilizing GnRH antagonist in treating hot flashes. One of ordinary skill in the art would have been motivated to do so because Furuya teaches utilizing gonadotropin releasing hormone antagonists in treating conditions exaggerated by sex hormones and instant specification teaches that it was known in the art that increasing GnRH level was involved in manifestation of hot flash and an antagonist of GnRH might help in suppressing it (Brain Research 754 (1997) 88-94.). Since Furuya teaches treating diseases exaggerated by sex hormone by utilizing GnRH antagonist and instant specification teaches over expresssion of GnRH during hot flashes and Takayoshi teaches utilizing GnRH antagonist in treating hot flashes, one would have been motivated to utilize compounds taught by Furuya in suppressing GnRH production and hence treating hot flashes.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in treating hot flashes which is caused by increased level of GnRH by utilizing the gonadotropin releasing hormone antagonist compounds of Furuya et al. with an expectation of suppressing the production of GnRH caused during hot flashes. The invention thus would have been obvious to one of ordinary skill in the art at the time the invention was made.

7. Claims 2-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuya et al. (US 6,048,863) in view of Takayoshi et al. (Brain Research, 754 (1997) 88-94. (Submitted in IDS) and further in view of applicants admission in instant specification page 3.

Furuya et al. teach a method for treating disorders related to gonadotropin releasing hormone (GnRH) comprising administering a thienopyrimidine derivative of the formula:



(abstract).

The thienopyrimidine derivative antagonizes gonadotropin-releasing hormone (column 2, lines 56-57).

Regarding hot flash as recited in instant claim 7, Furuya et al. teach a method of treating disorders related to gondotropin releasing hormone (abstract).

Furuya et al references teach that the disclosed compounds are useful for preventing and/or treating sex hormone-dependent cancers, prostatic hypertrophy, hysteromyoma, endometriosis, precocious puberty, amenorrhea, premenstrual syndrome, multiocular ovary syndrome and acne, which are conditions that are caused, **exaggerated** or maintained by sex hormones. In other words, the conditions taught by the Furuya et al references are conditions **where sex hormones are increased.**

Furuya et al. do not specifically teach treating hot flashes, Takayoshi et al. teaches gonadotropin-releasing hormone antagonism and its relation with treatment of hot flashes with such agents (see the whole article and the following paragraph).

Takayoshi et al. teach:

> Gonadotropin releasing hormone (GnRH), synthesized in the hypothalamus and secreted into the portal vein in the median eminence, plays important roles in regulating the menstrual cycle [9] and promoting lordosis behavior [23].

it is the GnRH that is thought to play a critical role in producing them [2,13]. Because skin vasodilation is a heat-dissipating thermoregulatory response and hot flushes tend to occur in the thermal condition in which normally skin vasodilation does not occur [3], hot flushes can be considered a malfunction of thermoregulation [13]. We therefore examined the central effects of GnRH on the thermoregulatory vasomotion of female rats. Both the hippocampus and septohypothalamic area contain high concentrations of GnRH receptors [1,8,13], but because the hippocampus does not seem to make a major contribution to thermoregulation [21], we focused on the effects of GnRH applied to the septal area and hypothalamus. All the rats in this work were ovariectomized to assure a stable hormonal condition, and we examined the central effects of GnRH not only on the skin vasodilation elicited by warming the preoptic area (PO) of anesthetized rats, but also on the skin vasomotion and core temperature of unanesthetized and unrestrained rats.

Takayoshi tests the effects of administering GnRH and Antide, an antagonist of GnRH on thermoregulatory skin vasomotion. Takayoshi teaches the treatment of hot flashes with a specific compound, i.e., Antide, which is an antagonist of GNRH. Thus the state of the art teaches that gonadotropin releasing hormone (GnRH) antagonist treats hot flashes.

Instant specification discloses lowering the sex hormone level decreases the negative feedback of the sex hormone and promotes synthesis and secretion of GnRH (gonadotropin releasing hormone). GnRH stimulates synthesis and secretion of LH and FSH to enhance their blood concentration. Therefore, various climacteric disorders including **hot flash may be caused by increase in the GnRH, LH or FSH level.** From an experiment of administration of GnRH or GnRH and an antagonist thereof into the brain of a rat, it was suggested that increasing GnRH level was involved in

manifestation of hot flash and an antagonist of GnRH might suppress it. (Brain Research 754 (1997) 88-94.) (See page 3).

It would have been obvious to one of ordinary skill in the art at the time of instant invention to utilize gonadotropin releasing hormone antagonists as taught by Furuya et al. in treating hot flashes because Takayoshi teaches utilizing GnRH antagonist in treating hot flashes. One of ordinary skill in the art would have been motivated to do so because Furuya teaches utilizing gonadotropin releasing hormone antagonists in treating conditions exaggerated by sex hormones and instant specification teaches that it was known in the art that increasing GnRH level was involved in manifestation of hot flash and an antagonist of GnRH might help in suppressing it (Brain Research 754 (1997) 88-94.). Since Furuya teaches treating diseases exaggerated by sex hormone by utilizing GnRH antagonist and instant specification teaches over expresssion of GnRH during hot flashes and Takayoshi teaches utilizing GnRH antagonist in treating hot flashes, one would have been motivated to utilize compounds taught by Furuya in suppressing GnRH production and hence treating hot flashes.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in treating hot flashes which is caused by increased level of GnRH by utilizing the gonadotropin releasing hormone antagonist compounds of Furuya et al. with an expectation of suppressing the production of GnRH caused during hot flashes. The invention thus would have been obvious to one of ordinary skill in the art at the time the invention was made.

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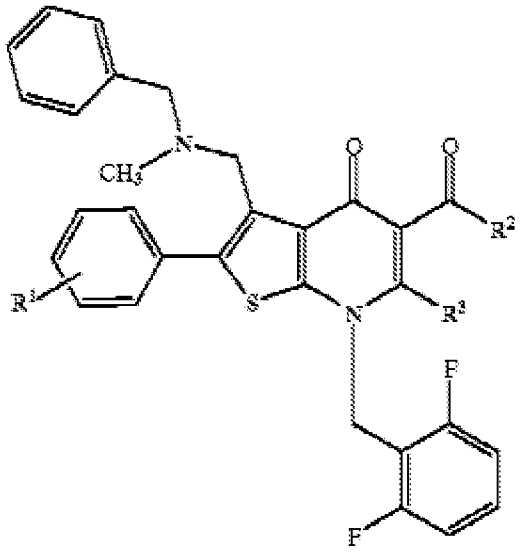
Furuya et al. teach a method for treating sex hormone dependent diseases comprising administering a thienopyridine derivative having gonadotropin-releasing hormone antagonistic activity of the formula:



(abstract and column 36, lines 5-20). The thienopyridine derivative has gonadotropin-releasing hormone antagonistic activity (abstract).

Furuya et al references teach that the disclosed compounds are useful for preventing and/or treating sex hormone-dependent cancers, prostatic hypertrophy, hysteromyoma, endometriosis, precocious puberty, amenorrhea,

premenstrual syndrome, multiocular ovary syndrome and acne, which are conditions that are caused, **exaggerated** or maintained by sex hormones. In other words, the conditions taught by the Furuya et al references are conditions **where sex hormones are increased.**

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treats hot flashes.

Instant specification discloses lowering the sex hormone level decreases the negative feedback of the sex hormone and promotes synthesis and secretion of GnRH (gonadotropin releasing hormone). GnRH stimulates synthesis and secretion of LH and FSH to enhance their blood concentration. Therefore, various climacteric disorders including **hot flash may be caused by increase in the GnRH, LH or FSH level.** From an experiment of administration of GnRH or GnRH and an antagonist thereof into the brain of a rat, it was suggested that increasing GnRH level was involved in manifestation of hot flash and an antagonist of GnRH might suppress it. (Brain Research 754 (1997) 88-94.) (See page 3).

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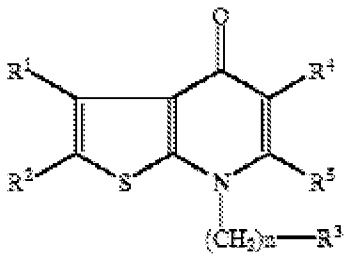
9. Claims 2-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuya et al. (US 6,187,788) in view of Takayoshi et al. (Brain Research, 754 (1997) 88-94 (submitted in IDS) and further in view of applicants admission in instant specification page 3.

Furuya et al. teach a method of treating a hormone dependent disease comprising administering a gonadotropin-releasing hormone antagonistic composition comprising a compound of the formula:



(abstract and column 116, lines 30-38).

Furuya et al references teach that the disclosed compounds are useful for preventing and/or treating sex hormone-dependent cancers, prostatic hypertrophy, hysteromyoma, endometriosis, precocious puberty, amenorrhea,

premenstrual syndrome, multiocular ovary syndrome and acne, which are conditions that are caused, **exaggerated** or maintained by sex hormones. In other words, the conditions taught by the Furuya et al references are conditions **where sex hormones are increased.**

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> it is the GnRH that is thought to play a critical role in producing them [2,13]. Because skin vasodilation is a heat-dissipating thermoregulatory response and hot flushes tend to occur in the thermal condition in which normally skin vasodilation does not occur [3], hot flushes can be considered a malfunction of thermoregulation [13]. We therefore examined the central effects of GnRH on the thermoregulatory vasomotion of female rats. Both the hippocampus and septohypothalamic area contain high concentrations of GnRH receptors [1,8,13], but because the hippocampus does not seem to make a major contribution to thermoregulation [21], we focused on the effects of GnRH applied to the septal area and hypothalamus. All the rats in this work were ovariectomized to assure a stable hormonal condition, and we examined the central effects of GnRH not only on the skin vasodilation elicited by warming the preoptic area (PO) of anesthetized rats, but also on the skin vasomotion and core temperature of unanesthetized and unrestrained rats.

Takayoshi tests the effects of administering GnRH and Antide, an antagonist of GnRH on thermoregulatory skin vasomotion. Takayoshi teaches the treatment of hot flashes with a specific compound, i.e., Antide, which is an antagonist of GNRH. Thus

the state of the art teaches that gonadotropin releasing hormone (GnRH) antagonist treats hot flashes.

Instant specification discloses lowering the sex hormone level decreases the negative feedback of the sex hormone and promotes synthesis and secretion of GnRH (gonadotropin releasing hormone). GnRH stimulates synthesis and secretion of LH and FSH to enhance their blood concentration. Therefore, various climacteric disorders including **hot flash may be caused by increase in the GnRH, LH or FSH level.** From an experiment of administration of GnRH or GnRH and an antagonist thereof into the brain of a rat, it was suggested that increasing GnRH level was involved in manifestation of hot flash and an antagonist of GnRH might suppress it. (Brain Research 754 (1997) 88-94.) (See page 3).

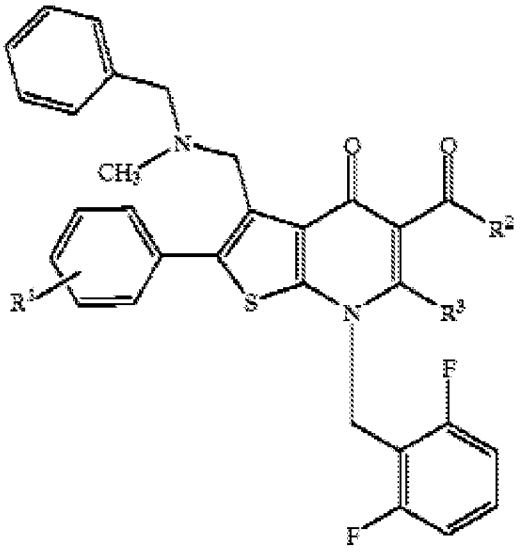
It would have been obvious to one of ordinary skill in the art at the time of instant invention to utilize gonadotropin releasing hormone antagonists as taught by Furuya et al. in treating hot flashes because Takayoshi teaches utilizing GnRH antagonist in treating hot flashes. One of ordinary skill in the art would have been motivated to do so because Furuya teaches utilizing gonadotropin releasing hormone antagonists in treating conditions exaggerated by sex hormones and instant specification teaches that it was known in the art that increasing GnRH level was involved in manifestation of hot flash and an antagonist of GnRH might help in suppressing it (Brain Research 754 (1997) 88-94.). Since Furuya teaches treating diseases exaggerated by sex hormone by utilizing GnRH antagonist and instant specification teaches over expresssion of GnRH during hot flashes and Takayoshi teaches utilizing GnRH antagonist in treating hot

flashes, one would have been motivated to utilize compounds taught by Furuya in suppressing GnRH production and hence treating hot flashes.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in treating hot flashes which is caused by increased level of GnRH by utilizing the gonadotropin releasing hormone antagonist compounds of Furuya et al. with an expectation of suppressing the production of GnRH caused during hot flashes. The invention thus would have been obvious to one of ordinary skill in the art at the time the invention was made.

10. Claims 2-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furuya et al. (US 6,001,850) in view of Garnick et al. (WO 99/55358) and further in view of Applicants admission in instant specification on page 3.

Furuya et al. teach a method for treating sex hormone dependent diseases comprising administering a thienopyridine derivative having gonadotropin-releasing hormone antagonistic activity of the formula:



(See abstract and column 36, lines, 5-20).

The thienopyridine derivative has gonadotropin-releasing hormone antagonistic activity (abstract).

Furuya et al references teach that the disclosed compounds are useful for preventing and/or treating sex hormone-dependent cancers, prostatic hypertrophy, hysteromyoma, endometriosis, precocious puberty, amenorrhea, premenstrual syndrome, multiocular ovary syndrome and acne, which are conditions that are caused, **exaggerated** or maintained by sex hormones. In other words, the conditions taught by the Furuya et al references are conditions **where sex hormones are increased.**

Furuya et al. do not specifically teach treating hot flashes

Garnick et al. teaches methods to inhibit hot flashes in a subject by administering an LHRH antagonist to a subject in need for treatment of hot flashes such that hot flashes are inhibited in the subject, see abstract. Thus state of the art teaches that LHRH antagonist (which is same as GHRH antagonist) helps in treating hot flashes.

Instant specification discloses lowering the sex hormone level decreases the negative feedback of the sex hormone and promotes synthesis and secretion of GnRH (gonadotropin releasing hormone). GnRH stimulates synthesis and secretion of LH and FSH to enhance their blood concentration. Therefore, various climacteric disorders including **hot flash may be caused by increase in the GnRH, LH or FSH level.** From an experiment of administration of GnRH or GnRH and an antagonist thereof into the brain of a rat, it was suggested that increasing GnRH level was involved in manifestation of hot flash and an antagonist of GnRH might suppress it. (Brain Research 754 (1997) 88-94.) (See page 3).

It would have been obvious to one of ordinary skill in the art at the time of instant invention to utilize gonadotropin releasing hormone antagonists as taught by Furuya et al. in treating hot flashes because Garnick et al. teach utilizing LHRH (which is also GnRH) in treating hot flashes. One of ordinary skill in the art would have been motivated to do so because Furuya teaches utilizing gonadotropin releasing hormone antagonists in treating conditions exaggerated by sex hormones and instant specification teaches that it was known in the art that increasing GnRH level was involved in manifestation of hot flash and an antagonist of GnRH might help in suppressing it (Brain Research 754 (1997) 88-94.).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in treating hot flashes which is caused by increased level of GnRH by utilizing the gonadotropin releasing hormone antagonist compounds of Furuya et al. with an expectation of suppressing the

production of GnRH caused during hot flashes. The invention thus would have been obvious to one of ordinary skill in the art at the time the invention was made.

Response to arguments

11. Applicant's arguments with respect to claims 2-3 and 5-7 have been considered but are moot in view of the new ground(s) of rejection.

CITED AS INTEREST

The following reference deals with GnRH manifestation during hot flashes.
(Brain Research 754 (1997) 88-94.) (See page 3).

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S Kishore/

Primary Examiner, Art Unit 1612